ORIGINAL ARTICLE

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Enhancing tumor-specific T-cell immunity by inhibiting programmed death ligand 1 (PD-L1)–programmed death 1 (PD-1) signaling has shown promise in the treatment of extensive-stage small-cell lung cancer. Combining checkpoint inhibition with cytotoxic chemotherapy may have a synergistic effect and improve efficacy.

METHODS

We conducted this double-blind, placebo-controlled, phase 3 trial to evaluate atezolizumab plus carboplatin and etoposide in patients with extensive-stage small-cell lung cancer who had not previously received treatment. Patients were randomly assigned in a 1:1 ratio to receive carboplatin and etoposide with either atezolizumab or placebo for four 21-day cycles (induction phase), followed by a maintenance phase during which they received either atezolizumab or placebo (according to the previous random assignment) until they had unacceptable toxic effects, disease progression according to Response Evaluation Criteria in Solid Tumors, version 1.1, or no additional clinical benefit. The two primary end points were investigator-assessed progression-free survival and overall survival in the intention-to-treat population.

RESULTS

A total of 201 patients were randomly assigned to the atezolizumab group, and 202 patients to the placebo group. At a median follow-up of 13.9 months, the median overall survival was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio for death, 0.70; 95% confidence interval [CI], 0.54 to 0.91; P=0.007). The median progression-free survival was 5.2 months and 4.3 months, respectively (hazard ratio for disease progression or death, 0.77; 95% CI, 0.62 to 0.96; P=0.02). The safety profile of atezolizumab plus carboplatin and etoposide was consistent with the previously reported safety profile of the individual agents, with no new findings observed.

CONCLUSIONS

The addition of atezolizumab to chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. (Funded by F. Hoffmann–La Roche/Genentech; IMpower133 ClinicalTrials.gov number, NCT02763579.)

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*A complete list of investigators in the IMpower133 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Standard-of-care first-line treatment for extensive-stage small-cell lung cancer is platinum chemotherapy (carboplatin or cisplatin) with etoposide.[1-3] Despite response rates of 60 to 65%, limited progress has been made in more than two decades; outcomes remain poor, with a median overall survival of approximately 10 months.[3,4] Small-cell lung cancer has a high mutation rate, which suggests that these tumors may be immunogenic and could respond to immune-checkpoint inhibitors.[5-7] Adding immunotherapy to chemotherapy may enhance antitumor immunity and improve outcomes beyond those achieved with our current therapeutic armamentarium. Clinical activity of immunotherapies has been observed in patients with refractory or metastatic small-cell lung cancer[8-12]; however, a phase 2 single-group study of maintenance pembrolizumab and a phase 3 study of ipilimumab plus chemotherapy showed no improved efficacy in the first-line treatment of extensive-stage small-cell lung cancer.[12,13]

Atezolizumab (Tecentriq, F. Hoffmann–La Roche/Genentech) is a humanized monoclonal anti–programmed death ligand 1 (PD-L1) antibody that inhibits PD-L1–programmed death 1 (PD-1) and PD-L1–B7-1 signaling and restores tumor-specific T-cell immunity.[14,15] In a phase 1 trial, atezolizumab monotherapy had an acceptable side-effect and safety profile, with promising durability of response in patients with relapsed or refractory small-cell lung cancer.[10]

The IMpower133 trial evaluated the efficacy and safety of adding atezolizumab or placebo to first-line treatment with carboplatin and etoposide in patients with extensive-stage small-cell lung cancer. We report a planned interim analysis of overall survival and a final analysis of progression-free survival.

Methods

Trial Oversight

F. Hoffmann–La Roche/Genentech sponsored the IMpower133 trial, provided the trial drugs, and collaborated with the academic authors on the design of the trial and on the collection, analysis, and interpretation of the data. The trial was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. All patients provided written informed consent. An independent data and safety monitoring committee reviewed safety data regularly. Protocol approval was obtained from an independent ethics committee at each site. The protocol is available with the full text of this article at NEJM.org. An author who is an employee of F. Hoffmann–La Roche and an author who is an employee of Genentech analyzed the data. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All drafts of the manuscript were prepared by the authors, with editorial and writing assistance funded by the sponsor.

A Quick Take is available at NEJM.org

Patients

Eligible patients were adults with histologically or cytologically confirmed extensive-stage small-cell lung cancer as defined according to the Veterans Administration Lung Study Group staging system (Table S1 in the Supplementary Appendix, available at NEJM.org),[16] measurable extensive-stage small-cell lung cancer according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers reflecting greater disability) who had not received previous systemic treatment for extensive-stage small-cell lung cancer. Patients with treated asymptomatic central nervous system metastases were eligible (see the Supplementary Methods section in the Supplementary Appendix). Key exclusion criteria were a history of autoimmune disease and previous treatment with CD137 agonists or immune-checkpoint blockade therapies.

Trial Design and Interventions

The IMpower133 trial is a multinational, phase 1 (safety) and phase 3 (efficacy), double-blind, randomized, placebo-controlled trial. Enrolled patients were assigned in a 1:1 ratio to receive, in the induction phase, four 21-day cycles of carboplatin (area under the curve of 5 mg per milliliter per minute, administered intravenously on day 1 of each cycle) and etoposide (100 mg per square meter of body-surface area, administered intravenously on days 1 through 3 of each cycle) with either atezolizumab (at a dose of 1200 mg, administered intravenously on day 1 of each cycle) or placebo (Fig. S1 in the Supplementary Appen-

dix). The induction phase was followed by a maintenance phase during which patients received either atezolizumab or placebo (according to the previous random assignment) until the occurrence of unacceptable toxic effects or disease progression according to RECIST. Continuation of the trial regimen after the occurrence of disease progression during either phase was allowed if evidence of clinical benefit existed (see the Supplementary Methods section in the Supplementary Appendix). During the maintenance phase, prophylactic cranial irradiation was permitted, but thoracic radiation therapy was not. Randomization was performed with the use of a permuted-block randomization method (IxRS) and was stratified according to sex, ECOG performance-status score (0 or 1), and presence of brain metastases (yes or no). PD-L1 testing was not performed during screening owing to the expected high rate of inadequate sample types (e.g., fine-needle aspirates, bronchoscopy findings), the low prevalence of PD-L1 expression on tumor cells, and the lack of an association between response and PD-L1 expression in the phase 1 trial of atezolizumab in extensive-stage small-cell lung cancer.[8-10,17,18]

Phase 1 of the trial was a safety run-in period to establish the side-effect and adverse-event profile of the treatment regimens; during this phase, a minimum of 12 patients were assigned to each group and received at least two cycles of treatment. Trial treatments were administered at full dose according to the protocol. Unblinded safety data were reviewed by an independent data and safety monitoring committee for assessment of the side-effect profile; on the basis of the findings of the committee, the trial continued as a randomized phase 3 trial.

END POINTS AND ASSESSMENTS

The primary end points were overall survival (the time from randomization to death from any cause) and investigator-assessed progression-free survival (the time from randomization to disease progression according to RECIST or death from any cause, whichever occurred first) in the intention-to-treat population. Key secondary end points included investigator-assessed objective response rate (according to RECIST) and the duration of response. Confirmation of responses was not required per protocol, but confirmed response rates were reported in the interest of rigor and to protect against potential bias. The estimated rate of overall survival at 1 year was evaluated. Exploratory analyses included the assessment of efficacy according to tumor mutational burden. Assessments of tumor mutational burden were performed with the use of a blood-based assay (blood-based tumor mutational burden), as reported previously.[19]

Tumor assessments were conducted at screening, every 6 weeks for the first 48 weeks starting from day 1 of cycle 1, and every 9 weeks thereafter until the occurrence of disease progression according to RECIST. Patients who continued the trial regimen beyond disease progression continued to undergo tumor assessments every 6 weeks until the regimen was discontinued. Adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The investigators determined whether adverse events were related to the trial regimen.

STATISTICAL ANALYSIS

The primary end points were assessed in the intention-to-treat population and were analyzed according to the assigned treatment, regardless of the actual treatment received. For the analysis of progression-free survival, data for patients who were alive and had no disease progression were censored at the time of the last tumor assessment. For the analysis of overall survival, data for patients who were alive were censored at the time of the last contact.

To control the overall two-sided type I error rate of 0.05, a group-sequential weighted Holm procedure[20,21] was used wherein the two-sided significance levels of 0.005 and 0.045 were allocated to the primary comparisons for progression-free survival and overall survival, respectively. The test that was significant could pass its alpha level to the test that was not statistically significant at the original allocated alpha level.

The sample size of the trial was determined by the analysis of overall survival. We calculated that 306 deaths in the intention-to-treat population would be needed to provide 91% power at a two-sided significance level of 0.045 to detect a hazard ratio for death with atezolizumab as compared with placebo of 0.68, with the use of a log-rank test. One interim analysis of overall

survival was performed when 238 deaths had occurred (the data cutoff date was April 24, 2018), with a two-sided alpha level of 0.0193 (stopping boundary), computed on the basis of the Lan–DeMets function approximating the O'Brien–Fleming boundary.[22]

The primary analysis of progression-free survival was conducted at the time of the interim analysis of overall survival. No interim analysis of progression-free survival was planned.

The stratified log-rank test (stratified according to sex and ECOG performance-status score [0 or 1]) was used for the primary analysis. As prespecified in the statistical analysis plan, the stratification factor that contained the level with the smallest size was dropped from the stratified analysis if at least one stratum had fewer than 10 events. As a result, the stratification factor of presence or absence of brain metastases was removed from the stratified analysis because it contained the level with the lowest number of patients.

Kaplan–Meier methodology was used to estimate the probability of overall survival and progression-free survival, as well as to calculate the median time from randomization to death (for overall survival) and the median time from randomization to disease progression or death (for progression-free survival) for each group, and the Brookmeyer and Crowley method was used to construct the 95% confidence interval for the medians.[23] A similar approach was used for the analysis of the duration of response. The hazard ratios and 95% confidence intervals for overall survival and progression-free survival were estimated with the use of a stratified Cox regression model, with the same stratification factors that were used in the stratified log-rank test.

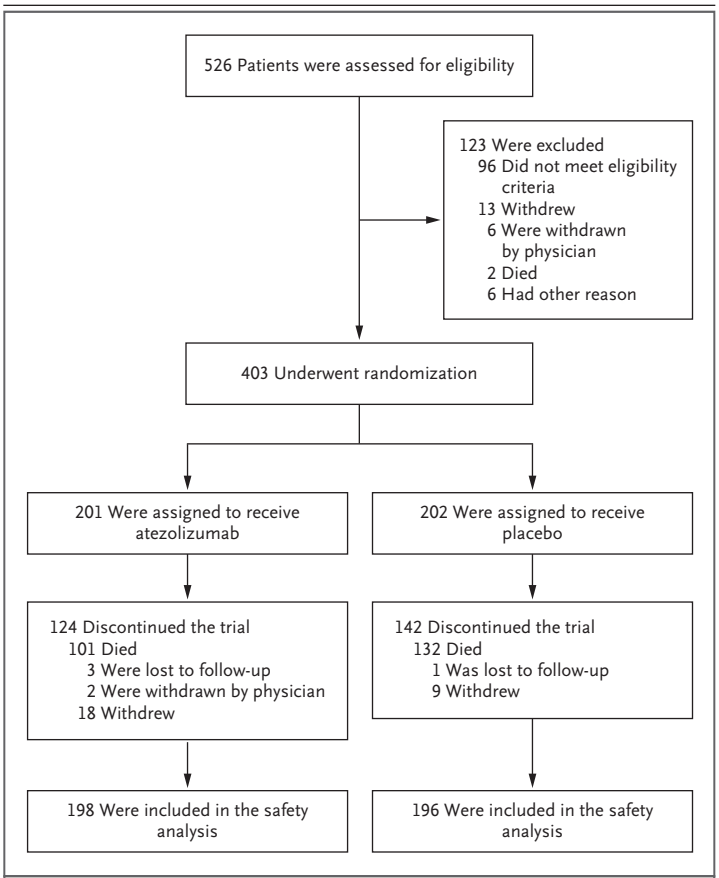


Figure 1. Eligibility, Randomization, and Analysis.

All patients who underwent randomization were included in the intention-to-treat analysis regardless of actual treatment received and duration of treatment or follow-up. Patients were randomly assigned to receive atezolizumab plus carboplatin and etoposide (atezolizumab group) or placebo plus carboplatin and etoposide (placebo group); four 21-day cycles of treatment were administered in the induction phase, after which patients received atezolizumab or placebo in a maintenance phase. One patient assigned to the placebo group received a dose of atezolizumab and was included in the atezolizumab group in the safety analyses. The date of data cutoff was April 24, 2018.

RESULTS

PATIENTS

Between June 6, 2016, and May 31, 2017, a total of 403 patients were enrolled at 106 sites in 21 countries and were randomly assigned to the atezolizumab group (201 patients) or the placebo group (202 patients) (Fig. 1). Baseline characteristics were well balanced between the groups (Table 1, and Tables S2 and S3 in the Supplementary Appendix). Twenty-two patients in each group received prophylactic cranial irradiation.

In the intention-to-treat population, 104 patients in the atezolizumab group and 116 in the placebo group received at least one subsequent therapy (Table S4 in the Supplementary Appendix). Fifteen patients in the placebo group received subsequent immunotherapy.

OVERALL SURVIVAL ANALYSIS

At the time of data cutoff, the median follow-up was 13.9 months. A total of 104 patients (51.7%) in the atezolizumab group and 134 patients

Table 1. Baseline Characteristics of All Enrolled Patients (Intention-to-Treat Population).*

Characteristic	Atezolizumab Group (N=201)	Placebo Group (N=202)
Median age (range) — yr	64 (28–90)	64 (26–87)
Age group — no. (%)		
<65 yr	111 (55.2)	106 (52.5)
≥65 yr	90 (44.8)	96 (47.5)
Male sex — no. (%)†	129 (64.2)	132 (65.3)
ECOG performance-status score — no. (%)†‡		
0	73 (36.3)	67 (33.2)
1	128 (63.7)	135 (66.8)
Smoking status — no. (%)		
Never smoked	9 (4.5)	3 (1.5)
Current smoker	74 (36.8)	75 (37.1)
Former smoker	118 (58.7)	124 (61.4)
Brain metastasis at enrollment — no. (%)†	17 (8.5)	18 (8.9)
Blood-based tumor mutational burden — no./total no. (%)§		
<10 mutations/Mb	71/173 (41.0)	68/178 (38.2)
≥10 mutations/Mb	102/173 (59.0)	110/178 (61.8)
<16 mutations/Mb	133/173 (76.9)	138/178 (77.5)
≥16 mutations/Mb	40/173 (23.1)	40/178 (22.5)
Median sum of longest diameter of target lesions at baseline (range)	113.0 (12.0–325.0)	105.5 (15.0–353.0)
Previous anticancer treatments — no. (%)		
Chemotherapy or nonanthracycline¶	8 (4.0)	12 (5.9)
Radiotherapy	25 (12.4)	28 (13.9)
Cancer-related surgery	33 (16.4)	25 (12.4)

* The date of data cutoff was April 24, 2018.
† The data were determined from electronic case-report forms.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability.
§ Of the 403 patients in the two groups, 374 had plasma available for blood-based analysis of tumor mutational burden; 351 of the samples (173 in the atezolizumab group and 178 in the placebo group) yielded high-quality data for analysis of tumor mutational burden.
¶ Previous chemotherapy or nonanthracycline treatments included cisplatin, etoposide, and concurrent radiation (in six patients in the atezolizumab group and seven patients in the placebo group) and carboplatin, etoposide, and concurrent radiation (in two patients in the atezolizumab group and six patients in the placebo group).

(66.3%) in the placebo group had died. Overall survival was significantly longer in the atezolizumab group (median, 12.3 months; 95% confidence interval [CI], 10.8 to 15.9) than in the placebo group (median, 10.3 months; 95% CI, 9.3 to 11.3). The stratified hazard ratio for death was 0.70 (95% CI, 0.54 to 0.91; P=0.007) (Fig. 2A), and the 1-year overall survival rate was 51.7% in the atezolizumab group and 38.2% in the placebo group.

PROGRESSION-FREE SURVIVAL ANALYSIS

A total of 171 patients (85.1%) in the atezolizumab group and 189 patients (93.6%) in the placebo group had disease progression or died. Progression-free survival was longer in the atezolizumab group (median, 5.2 months; 95% CI, 4.4 to 5.6) than in the placebo group (median, 4.3 months; 95% CI, 4.2 to 4.5). The stratified hazard ratio for disease progression or death was 0.77 (95% CI, 0.62 to 0.96; P=0.02) (Fig. 2B).

SURVIVAL OUTCOMES IN SELECTED PATIENT SUBGROUPS

The benefit with respect to overall survival and progression-free survival associated with the addition of atezolizumab was consistent across key subgroups. Of the 403 patients in the two groups, 374 had plasma available for blood-based analysis of tumor mutational burden; 351 of the samples (93.8%) yielded high-quality data for analysis of tumor mutational burden. An exploratory analysis showed a consistent overall survival and progression-free survival benefit above and below the prespecified cutoffs of 10 and 16 mutations per megabase (Fig. 2C, and Fig. S2 in the Supplementary Appendix).

CONFIRMED OBJECTIVE RESPONSE RATE AND DURATIONS OF RESPONSE

Investigator-assessed confirmed objective response rates and median duration of response were similar in the two groups (Table 2, and Table S5 in the Supplementary Appendix). In total, five patients (2.5%) in the atezolizumab group and two patients (1.0%) in the placebo group had a complete response.

SAFETY

The population that could be evaluated for safety included 198 patients who received at least 1 dose of atezolizumab and 196 patients who received placebo. The median duration of treatment with atezolizumab was 4.7 months (range, 0 to 21), and the median number of atezolizumab doses received was 7 (range, 1 to 30). The median number of doses of chemotherapy was the same in the two groups (median, 4 doses of carboplatin and 12 doses of etoposide). The median dose intensity and total cumulative dose of chemotherapy were similar in the two groups (Table S6 in the Supplementary Appendix).

Adverse events related to any component of the trial regimen occurred in 188 patients (94.9%) in the atezolizumab group and in 181 patients (92.3%) in the placebo group. The most common grade 3 or 4 adverse events related to the trial regimen were neutropenia, anemia, and decreased neutrophil count (Table 3).

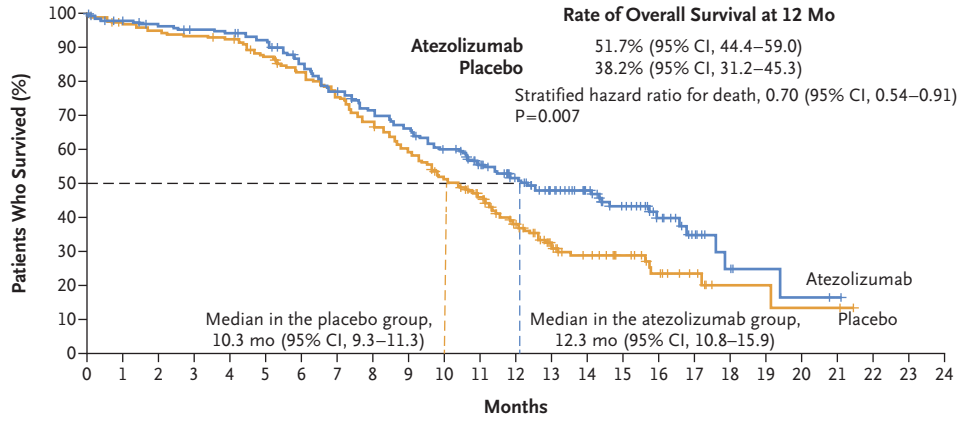
Deaths related to the trial regimen occurred in 3 patients (1.5%) in the atezolizumab group (death was due to neutropenia in 1 patient, pneumonia in 1 patient, and an unspecified cause in 1 patient) and in 3 patients (1.5%) in the placebo group (death was due to pneumonia in 1 patient, septic shock in 1 patient, and cardiopulmonary failure in 1 patient). Immune-related adverse events occurred in 79 patients (39.9%) in the atezolizumab group and in 48 patients (24.5%) in the placebo group, with rash and hypothyroidism being the most common. Additional information on adverse events is provided in Tables S7 through S10 in the Supplementary Appendix.

DISCUSSION

At the time of the primary analysis of progression-free survival and the interim analysis of overall survival, this randomized, placebo-controlled, phase 3 trial showed that the addition of atezolizumab to carboplatin and etoposide resulted in significantly longer overall and progression-free survival than chemotherapy alone. The median overall survival was 2 months longer in the atezolizumab group than in the placebo group, and the 1-year overall survival rate was approximately 13 percentage points higher in the atezolizumab group than in the placebo group (51.7% vs. 38.2%). Benefits with respect to overall survival and progression-free survival were consistent across patient subgroups. Objective response rates and median duration of response were similar in the two groups; however, more patients in the atezolizumab group than in the placebo group had an ongoing response at the time of data cutoff (Table 2, and Table S5 in the Supplementary Appendix).

In patients with treated brain metastases, no difference between the two groups was observed in overall survival or progression-free survival. Owing to the small number of patients with brain metastases enrolled in the trial and the exploratory nature of the analysis, no conclusions can be drawn. Further trials are needed to investigate the role of immunotherapy in patients with small-cell lung cancer who have brain metastases. An imbalance in overall survival benefit appeared to be present among patients younger than 65 years of age, with older patients faring better. There is no simple biologic explanation for this observation, and further analyses are needed to understand whether other factors may have contributed to this result.

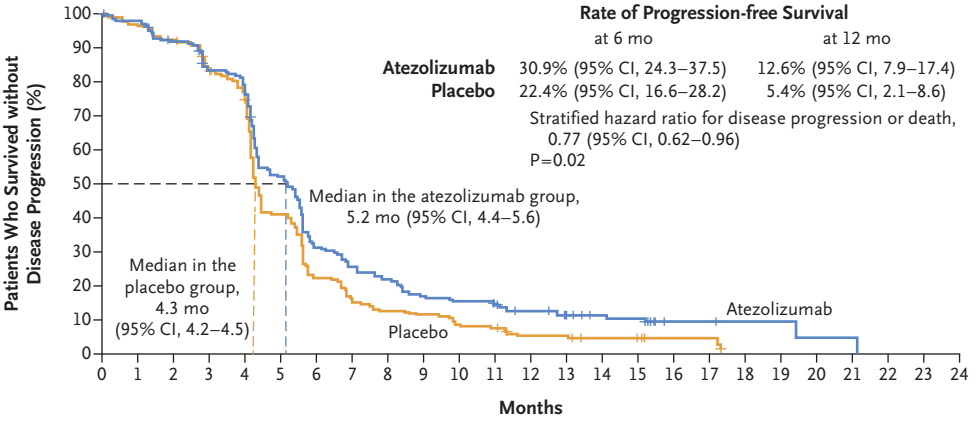
A Overall Survival



No. at Risk

Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

B Progression-free Survival



No. at Risk

Atezolizumab	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1
Placebo	202	193	184	167	147	80	44	30	25	23	16	15	9	9	6	5	3	3				

C Overall Survival According to Baseline Characteristics

Subgroup	No. of Patients (%)	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Atezolizumab	Placebo	
Sex				
Male	261 (65)	12.3	10.9	0.74 (0.54–1.02)
Female	142 (35)	12.5	9.5	0.65 (0.42–1.00)
Age				
<65 yr	217 (54)	12.1	11.5	0.92 (0.64–1.32)
≥65 yr	186 (46)	12.5	9.6	0.53 (0.36–0.77)
ECOG score				
0	140 (35)	16.6	12.4	0.79 (0.49–1.27)
1	263 (65)	11.4	9.3	0.68 (0.50–0.93)
Brain metastases				
Yes	35 (9)	8.5	9.7	1.07 (0.47–2.43)
No	368 (91)	12.6	10.4	0.68 (0.52–0.89)
Liver metastases				
Yes	149 (37)	9.3	7.8	0.81 (0.55–1.20)
No	254 (63)	16.8	11.2	0.64 (0.45–0.90)
Tumor mutational burden				
<10 mutations/Mb	139 (34)	11.8	9.2	0.70 (0.45–1.07)
≥10 mutations/Mb	212 (53)	14.6	11.2	0.68 (0.47–0.97)
<16 mutations/Mb	271 (67)	12.5	9.9	0.71 (0.52–0.98)
≥16 mutations/Mb	80 (20)	17.8	11.9	0.63 (0.35–1.15)
Intention-to-treat population	403 (100)	12.3	10.3	0.70 (0.54–0.91)

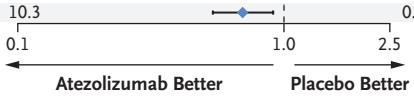


Table 2. Response Rate, Duration of Response, and Disease Progression.*

Variable	Atezolizumab Group (N = 201)	Placebo Group (N = 202)
Objective confirmed response†	121 (60.2 [53.1–67.0])	130 (64.4 [57.3–71.0])
Complete response — no. (% [95% CI])	5 (2.5 [0.8–5.7])	2 (1.0 [0.1–3.5])
Partial response — no. (% [95% CI])	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.0])
Median duration of response (range) — mo‡	4.2 (1.4§–19.5)	3.9 (2.0–16.1§)
Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (% [95% CI])	42 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.6])
Progressive disease — no. (% [95% CI])	22 (10.9 [7.0–16.1])	14 (6.9 [3.8–11.4])

* The date of data cutoff was April 24, 2018.
† The objective confirmed response rate was assessed in patients in the intention-to-treat population who had measurable disease at baseline. Objective response was defined as confirmed complete response or partial response as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.
‡ Duration of response was assessed in patients who had an objective confirmed response and was defined as the time from the first occurrence of a documented objective response to the time of disease progression as determined by the investigator (according to RECIST) or death from any cause, whichever occurred first.
§ Data for the lower range of the response in the atezolizumab group and the upper range of the response in the placebo group are censored.

Exploratory subgroup analyses showed no clear suggestion that blood-based tumor mutational burden levels at either cutoff (10 or 16 mutations per megabase) were predictive of benefit with atezolizumab in this population. These results are in contrast to previous studies that suggested an association between high tumor mutational burden and better clinical outcomes in patients receiving cancer immunotherapies.[24,25] A possible explanation for the lack of greater benefit with respect to clinical outcomes in patients with high blood-based tumor mutational burden in this trial is that the combination of platinum and etoposide is highly active and also highly myelosuppressive.

In this trial, exposure to chemotherapy was maintained with the addition of atezolizumab. Rates of hematologic side effects were similar in the two groups, and the incidence and types of immune-related adverse events were similar to those seen with atezolizumab monotherapy.[26-28]

One randomized, phase 3 study assessed an immunotherapy (ipilimumab) plus chemotherapy as compared with chemotherapy alone in the first-line treatment of patients with extensive-stage small-cell lung cancer, but no significant difference in overall survival between the two groups was noted.[13] Ipilimumab targets CTLA-4 and stimulates peripheral T-cell activation but does not activate T cells in the tumor microenvironment; given this mechanism of action, Reck and colleagues speculated that ipilimumab may be of limited value when added to chemotherapy in patients with this disease.[13] One possible explanation for the effectiveness of atezolizumab in addition to chemotherapy in the IMpower133 trial may be that carboplatin and etoposide might not deplete the intratumoral T-cell population, and atezolizumab may be able to activate the intratumoral T lymphocytes to exert an antitumor effect; however, further studies are needed to confirm this hypothesis.

In addition, a single-group, phase 2 study of maintenance pembrolizumab in extensive-stage small-cell lung cancer did not show longer progression-free survival or overall survival when compared with historical data.[12] In contrast, the current trial showed a significant improvement in progression-free survival and over-

Figure 2 (facing page). Overall Survival and Investigator-Assessed Progression-free Survival in the Intention-to-Treat Population.

Panel A shows the Kaplan–Meier estimates of overall survival, and Panel B the Kaplan–Meier estimates of investigator-assessed progression-free survival. Tick marks indicate censored data. Panel C shows a subgroup analysis of overall survival according to baseline characteristics. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability. Tumor mutational burden was assessed with the use of a blood-based assay.

Table 3. Adverse Events Related to the Trial Regimen.*

Event	Atezolizumab Group (N=198)			Placebo Group (N=196)		
	Grade 1 or 2	Grade 3 or 4	Grade 5	Grade 1 or 2	Grade 3 or 4	Grade 5
	number of patients (percent)					
Any adverse event	73 (36.9)	112 (56.6)	3 (1.5)	68 (34.7)	110 (56.1)	3 (1.5)
Adverse events with an incidence of ≥10% in any grade category or events of grade 3 or 4 with an incidence of ≥2% in either group						
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Alopecia	69 (34.8)	0	0	66 (33.7)	0	0
Nausea	62 (31.3)	1 (0.5)	0	58 (29.6)	1 (0.5)	0
Fatigue	39 (19.7)	3 (1.5)	0	37 (18.9)	1 (0.5)	0
Decreased neutrophil count	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Decreased appetite	39 (19.7)	2 (1.0)	0	26 (13.3)	0	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Decreased platelet count	17 (8.6)	7 (3.5)	0	21 (10.7)	7 (3.6)	0
Vomiting	25 (12.6)	2 (1.0)	0	19 (9.7)	3 (1.5)	0
Constipation	19 (9.6)	1 (0.5)	0	25 (12.8)	0	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Decreased white-cell count	10 (5.1)	6 (3.0)	0	16 (8.2)	9 (4.6)	0
Diarrhea	15 (7.6)	4 (2.0)	0	18 (9.2)	1 (0.5)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0
Infusion-related reaction	6 (3.0)	4 (2.0)	0	9 (4.6)	1 (0.5)	0

* The date of data cutoff was April 24, 2018. Multiple occurrences of the same adverse event in one patient were counted once at the highest grade for the preferred term. The incidence of treatment-related adverse events associated with any component of the trial regimen is shown.

all survival with the addition of atezolizumab to chemotherapy as first-line treatment. This suggests that combining checkpoint inhibition with cytotoxic therapy during induction may be beneficial and potentially necessary to improve overall survival beyond that seen with the current standard of care, and thus it may be a preferred treatment approach over maintenance checkpoint-inhibitor therapy alone. Further studies directly comparing the two treatment approaches are needed.

In summary, this multinational trial in the first-line treatment of extensive-stage small-cell lung cancer in a patient population typical for this disease showed that the addition of atezolizumab to carboplatin and etoposide was associated with significantly longer overall survival and progression-free survival, with a safety profile consistent with the defined toxic effects of the individual agents.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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